Impact of Therapy With Epoetin Alfa on Clinical Outcomes in Patients With Nonmyeloid Malignancies During Cancer Chemotherapy in Community Oncology Practice

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Purpose: **To study the impact of Procrit (epoetin alfa; Amgen Inc, Thousand Oaks, CA) on quality of life, transfusion requirements, and hemoglobin in anemic cancer patients receiving chemotherapy.**

Patients and Methods: **More than 500 community-based oncologists enrolled 2,342 patients with malignancies undergoing cytotoxic chemotherapy in an open-label study. Patients were treated with epoetin alfa 150 U/kg three times weekly, which could be doubled if the therapuetic response was judged inadequate. Total treatment was up to 4 months.**

Results: **Of the 2,342 patients enrolled, data were available for 2,030 patients. Of the 2,030, 1,047 patients completed all 4 months of epoetin alfa therapy. Epoetin alfa was associated with significant increases in mean self-rated scores for energy level, activity level, and overall quality of life; these improvements correlated with the magnitude of the hemoglobin increase and were independent of tumor response. In addition, epoetin alfa was associated with a significant increase in mean hemoglobin and with a significant decrease in the proportion of patients requiring transfusions (baseline to final value, $P < .001$). Epoetin alfa was well tolerated.**

Conclusion: **Epoetin alfa is effective in improving the funtional status and quality of life in anemic cancer patients receiving chemotherapy, as well as increasing hemoglobin level and decreasing transfusion requirements. Improvement in functional status can be attributed to an increase in hemoglobin level, demonstrating that quality of life in this group of patients can be improved by aggressively treating anemia. Further studies will be required to define the optimal doses and schedules for epoetin alfa.**

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ANEMIA IS A FREQUENT complication of cancer chemotherapy in community oncology practice, and results in both a decreased functional capacity and quality of life for cancer patients and the necessity for RBC transfusions with the associated risks, inconvenience, and cost.[1] The etiology of this anemia has been considered multifactorial, with contributing factors including aberrant ferrokinetics associated with chronic disease, poor nutritional status, bleeding, and bone marrow infiltration with tumor. It has also been demonstrated that circulating endogenous erythropoietin levels are significantly lower in anemic cancer patients than in patients with a similar degree of anemia due to iron deficiency, which strongly suggests that a blunted erythropoietin response to anemia may play an important role in the development and persistence of anemia in cancer patients.[2,3] These studies demonstrated that the administration of cancer chemotherapy may further decrease the endogenous erythropoietin response to anemia in cancer patients, exacerbating both the anemia and the relative erythropoietin deficiency. These observations formed the rational basis for clinical trials of recombinant human erythropoietin in cancer patients and in cancer patients receiving cancer chemotherapy.[4]

Several clinical trials have studied the effects of the administration of epoetin alfa to anemic cancer patients receiving myelosuppressive chemotherapy. Studies have analyzed the effects of epoetin alfa during noncisplatin chemotherapy separately because of the potentially greater deleterious effect of cisplatin on endogenous erythropoietin production mediated by impairment of renal function.[5] In a phase I/II study, therapy with epoetin alfa 100 to 300 U/kg/d five times weekly was associated with an increased hemoglobin level in anemic cancer patients who received cyclic chemotherapy regimens that did not contain cisplatin.[6] In a multicenter, randomized, double-blind, placebo-controlled clinical trial, the administration of epoetin alfa 150 U/kg thrice weekly for 12 weeks to anemic cancer patients receiving cyclical chemotherapy that did not contain cisplatin resulted in a statistically significant increase in hematocrit, energy level, and ability to perform daily activities.[7] Also, the data suggested a trend toward decreased transfusion re-

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quirements in patients who received epoetin alfa compared with placebo during the second and third months of treatment (0.91 *v* 1.65 U per patient per month; $P = .056$).

Epoetin alfa has been shown to be effective in both preventing and treating the anemia associated with cisplatin therapy in animals.[8] In humans, the administration of epoetin alfa has been associated with a decreased incidence of significant anemia in patients receiving cisplatin-based chemotherapy.[9] Phase I/II studies suggested that epoetin alfa, given in doses of 50 to 200 U/kg thrice weekly, is effective in the treatment of the anemia associated with cisplatin therapy.[6,10,11] In a randomized, double-blind, placebo-controlled clinical trial that included 132 anemic cancer patients undergoing cyclic cisplatin-based chemotherapy, the administration of epoetin alfa 150 U/kg thrice weekly for 12 weeks was associated with a significantly increased hemoglobin concentration, energy level, activity level, and overall quality of life.[12,13] There was a trend in these data that suggested decreased transfusion requirements in patients who received epoetin alfa (1.2 *v* 2.0 U per patient per month during months 2 and 3; $P = .089$). When the data from the randomized study in patients receiving non–cisplatin-containing chemotherapy were pooled with these data, significantly fewer patients treated with epoetin alfa received RBC transfusions (27.8% *v* 45.5%; $P < .005$) and fewer units per patient were transfused (1.04 *v* 1.81 U per patient per month; $P = .009$) as compared with placebo patients.[4,7,12,13] In another randomized and placebo-controlled trial, the administration of epoetin alfa given at a dose of 100 U/kg thrice weekly for 9 weeks to cancer patients with anemia secondary to cisplatin therapy was associated with increased hemoglobin levels and a sixfold decrease in the mean number of transfusions required (0.3 *v* 1.8 U per patient over 9 weeks; $P = .01$).[14]

These data demonstrate that, under the conditions of a carefully controlled and monitored clinical trial in the setting of a clinical research institution, the administration of epoetin alfa to cancer patients receiving cytotoxic chemotherapy is associated with an increase in hemoglobin level, a decrease in transfusion requirements, and an increase in quality of life as measured by the patient's self-assessment of well-being and functional capacity. The impact of epoetin alfa on these end points has not been studied in large numbers of patients receiving cancer chemotherapy in the setting of community oncology practice in which most treatment decisions are made in accordance with the judgement of the individual clinician and are not dictated by protocol.

To study the effect of epoetin alfa on a large number of oncology patients in a community-based setting, an open-label study was conducted in more than 500 community-based oncology practices in the United States, involving 2,342 patients undergoing treatment for malignancy. A similarly designed study, ie, nonrandomized, open-label, multicenter, was conducted to demonstrate the effectiveness of epoetin alfa on quality of life in anemic patients receiving dialysis.[15] The goal of this study, as well as the present study, was to determine the impact of administration of epoetin alfa to large numbers of anemic patients on clinically relevant outcomes in the community setting, both to establish effectiveness and to provide a basis for future assessments of cost, taking into account the prescribing behavior of community practitioners. The present protocol provided treatment guidance for the selection and monitoring of patients that reflected the package insert provided with Procrit (Amgen Inc, Thousand Oaks, CA), the brand of epoetin alfa marketed in the United States for the treatment of anemia associated with cancer chemotherapy.

PATIENTS AND METHODS

Patients

A total of 2,342 patients were enrolled onto this clinical trial. Entry criteria included a diagnosis of a nonmyeloid malignancy, ongoing cytotoxic chemotherapy, expected survival of more than 6 months, and anemia. Patients were to be excluded if they had uncontrolled hypertension, comorbidities that could contribute to the anemia (iron or folate deficiencies, hemolysis, or gastrointestinal bleeding), or a known allergy to mammalian cell-derived products. All patients signed written informed consent. The protocol and the consent form were approved by a central institutional review board.

Study Protocol

Baseline information was obtained within the 10-day period before the first dose of epoetin alfa and included weight, blood pressure, histology and stage of malignancy, transfusion history within the 6 months before study entry, and prior and current chemotherapy and radiotherapy history. Required baseline laboratories included hemoglobin and hematocrit levels. Laboratory screening for iron or folate deficiency or for hemolysis were not required by protocol. The collection of baseline endogenous serum erythropoietin levels was optional, but based on data obtained in previous clinical studies,[4] and consistent with the product labeling, it was suggested that patients with serum erythropoietin levels greater than 200 mU/mL not be treated with epoetin alfa.

Patients were seen and evaluated monthly for 4 months. At each monthly visit, hemoglobin, hematocrit, blood pressure, transfusion information, changes in chemotherapy prescribed, and adverse experiences were recorded. At baseline and at each monthly visit, a reticulocyte count was suggested, but not required. In the intervals between these visits, hematocrit and blood pressure levels were to be monitored weekly until the hematocrit level was believed to be stable.

The recommended start dose of epoetin alfa was 150 U/kg, admin-

istered subcutaneously thrice weekly. If the response in terms of reduced transfusion requirements or increased hematocrit was not satisfactory in the estimate of the clinician after 8 weeks at this starting dose, the dose of epoetin alfa could be increased to 300 U/kg thrice weekly. If, on any determination during the study, the patient's hematocrit level was greater than 40%, epoetin alfa was to be withheld until the hematocrit level decreased to ≤ 36%. The dose of epoetin alfa was reduced by 25% when treatment was resumed and adjusted by the clinician to maintain the desired hematocrit level. Physicians were instructed to lower the dose of epoetin alfa similarly if a rapid increase in hematocrit level, defined as more than four percentage points in any 2-week period, occurred.

The effects of epoetin alfa on each patient's perception of quality of life was measured using a tool identical to that used in the large placebo-controlled phase III studies. Quality of life for each patient was measured using three quality-of-life (energy, daily activity, and overall quality of life) linear-analog scales (Fig 1).[16,17] Visual-analog scales are well established as valid and reliable measures.[18] The technique has been frequently applied in clinical trials settings.[17] Huskisson et al[19-22] reported high levels of reliability (> 0.90) and correlations between visual-analog scales and other measures of pain ranging from 0.71 to 0.89.

Before initiation of epoetin alfa and at the conclusion of therapy, all patients were asked to rate their energy level, ability to perform daily activities, and overall quality of life on a 100-mm visual-analog scale, the extremes of which represent the best possible and worst possible scores for that category. The patients scored their own perceptions of these parameters by placing a mark on a 100-mm line, where 0 is worst and 100 is best; the score for each parameter was the measurement, in millimeters, between the mark and the starting point of the line.

Tumor Response

While optimal interpretation of quality-of-life results is obtained with randomized controlled trials, quality-of-life outcomes can also be measured in nonrandomized or descriptive studies. In these cases, appropriate controls such as measures of cancer response are necessary to draw inferences concerning the relationship between treatment and quality-of-life outcomes.[23,24]

A retrospective analysis was conducted to evaluate the possible effect of tumor response on changes in quality-of-life scores. For this analysis, 1,498 patients had baseline and final quality-of-life scores available. A worksheet for each of these patients was sent to the treating physician. The worksheet included standard definitions for tumor response specific to each tumor type. Data from 759 patients were received.

Study Drug

Procrit was supplied by Ortho Biotech Inc (Raritan, NJ). Human erythropoietin is expressed in Chinese hamster ovary cells. The drug was open-label and supplied in single-use vials that contained 10,000

QUALITY OF LIFE*
LINEAR ANALOG SCALE ASSESSMENT

TO BE COMPLETED BY THE PATIENT

Three questions about how you felt during this past week are listed below. Please place a vertical mark on the line to indicate your answer. The position of the mark, somewhere between the two extremes, should reflect how you feel.

*If at all possible, please complete this assessment prior to administration of chemotherapy.

1. HOW WOULD YOU RATE YOUR ENERGY LEVEL DURING THE PAST WEEK?

Fig 1. Quality-of-life linear-analog scale assessment.

2. HOW WOULD YOU RATE YOUR ABILITY TO DO YOUR DAILY ACTIVITIES OVER THE PAST WEEK?

3. HOW WOULD YOU RATE YOUR OVERALL QUALITY OF LIFE DURING THE PAST WEEK?

U/mL in a buffered solution that contained human serum albumin 2.5 mg/mL. The study drug was provided free to the physician for the treatment of enrolled patients.

Data Analysis

Data were summarized using frequency counts and percents for discrete variables and descriptive statistics, including means, medians, and SDs for continuous variables. Changes between baseline and each monthly value for hemoglobin, hematocrit, and transfusion rate were analyzed using paired *t* tests. The magnitude of change in quality-of-life scores was also evaluated using effect size, which assesses mean change as a proportion of the SD.[19] Changes from baseline to termination quality-of-life scores were analyzed using paired *t* tests. Change from baseline and month 1, 2, 3, and 4 values for percent of patients transfused were analyzed using McNemar's χ^2 test. A simple linear correlation was performed using regression analysis to study the correlation of baseline serum erythropoietin level with the change in hemoglobin level during epoetin alfa therapy and the correlation of change in each quality-of-life measure with the change in hemoglobin level during epoetin alfa therapy. All tests were two-tailed with $P = .05$ and no adjustments were made for multiple comparisons. Regression analysis of change in quality-of-life parameters from baseline to termination using tumor response and change in hemoglobin level from baseline to final evaluation as terms in the regression model was also performed.

RESULTS

Of 2,342 patients enrolled, data were available for 2,030. For the remaining 312 patients, either no data or incomplete data were available; therefore, these patients were not included in the data base. Of 2,030 patients with available data, 1,047 completed 4 months of epoetin alfa therapy; the data were analyzed for all patients who received epoetin alfa, as well as for the subset of patients who completed therapy. Patient characteristics are listed in Table 1; these characteristics were similar for all treated patients, as well as for the subset of treatment completers. For all patients, the mean age was 62.2 years and 62% were female. The mean baseline hematocrit level was 27.5% and the mean hemoglobin level 9.2 g/dL. At baseline, 21.9% of patients had received RBC transfusions within the month before study entry. The mean number of units transfused per patient per month during this prestudy period was 0.57. The mean baseline overall quality-of-life score was 45 mm out of a possible 100 mm, suggestive of a self-perceived significant limitation in overall well-being. Baseline serum erythropoietin levels were not required by protocol, but were available for 770 patients (38%); in approximately 85% of these patients, the erythropoietin level was less than 200 mU/mL. The mean baseline erythropoietin level was 148 ± 333 mU/mL.

Twenty-three percent of treated patients had hematologic malignancies, which included lymphoma, multiple myeloma, Hodgkin's disease, and chronic lymphocytic leukemia. The remainder had solid tumors, including lung cancer (22%), breast cancer (18%), gynecologic malignancies (14%), gastrointestinal malignancies (6%), prostate cancer (4%), head and neck tumors (2%), bladder cancer (2%), pancreatic, esophageal, and renal cancers (1% each), and other cancers (6%). Of 2,030 epoetin alfa–treated patients, 99% received chemotherapy on study: 441 (22%) were receiving chemotherapy regimens that contained cisplatin, 355 (18%) were receiving regimens that contained carboplatin, and the remainder (60%) were receiving non–platinum-based cyclical chemotherapy regimens. The chemotherapy regimens received by the subset of patients who completed treatment was similar; 192 (18%) of these patients were treated with cisplatin. During the epoetin alfa study period, 58 treated patients (3%) received ≥ 1 month of concomitant radiotherapy.

Table 1. Baseline Patient Characteristics

Characteristic	All Patients (N = 2,030)	Completers (n = 1,047)
Sex		
Male	774	389
Female	1,256	658
Mean ± SD age, years	62.2 ± 13.3	62.1 ± 13.4
Mean ± SD hematocrit (%)	27.5 ± 3.9	27.7 ± 3.7
Mean ± SD hemoglobin (g/dL)	9.2 ± 1.3	9.3 ± 1.3
Percent transfused month −1*	21.9	20.9
Percent transfused months −4 to −1*	36.9	35.4
Mean ± SD units transfused month −1*	0.57 ± 1.20	0.52 ± 1.11
Mean ± SD overall quality-of-life score (mm on 100-mm scale)	45.0 ± 23.8	46.6 ± 24.3
Mean ± SD overall energy score (mm on 100-mm scale)	38.1 ± 21.3	40.0 ± 21.7
Mean ± SD overall activity score (mm on 100-mm scale)	39.2 ± 23.9	41.1 ± 23.9
Serum erythropoietin level (mU/mL)		
Mean	149	142
Median	64	62
SD	333	314
	(N = 770)	(n = 385)

*Prestudy.

Of 2,030 patients, 1,047 (52%) completed the 4-month study. The reasons for discontinuing epoetin alfa before 4 months and the adverse events reported during epoetin alfa therapy are listed in Tables 2 and 3. The reason for discontinuing epoetin alfa was usually due to complications of the underlying disease, such as death (13%) or intercurrent illnesses (5%). In only 6% of cases was discontinuation due to a perception of an inadequate therapeutic response, which suggests the relatively large proportion of patients who terminated therapy early did not skew the data for later months in favor of the study drug. Epoetin alfa was well tolerated; approximately 1% of patients were reported to have hypertension and in only 3% of treated patients was the drug discontinued because

of an adverse event. Of 2,030 patients, 37.4% self-administered epoetin alfa. Epoetin alfa was administered by a health care professional to 46.5% of patients and by a spouse or caregiver to the remaining 16.1%. The mean age of patients to whom epoetin alfa was administered by a health care professional was 65.3 years.

Hemoglobin Response

The mean hemoglobin level increased progressively and significantly over the 4 months of epoetin alfa therapy (Table 4). In the 2,019 patients with a baseline and final hemoglobin measurement, there was a 1.8-g/dL increase from baseline to final hemoglobin level ($P < .001$). A significant increase in hemoglobin level was observed in patients with hematologic, as well as nonhematologic malignancies. In both groups of patients, a statistically significant increase in hemoglobin level was observed from baseline to each monthly visit, as well as at the final visit ($P < .001$). Hemoglobin levels and the magnitude of the mean increase were comparable in both groups. There was no correlation between hemoglobin response and baseline erythropoietin level ($P = .294$, $r = .020$). Although no specific erythropoietin level can be stated above which patients would be unlikely to respond, based on data from previous double-blind studies, treatment of patients with levels greater than 200 mU/mL is not recommended. However, for patients who presented with baseline erythropoietin levels greater than 200 mU/mL and had hemoglobin data available, a statistically significant hemoglobin improvement from baseline to final value was demonstrated (mean, 8.4 g/dL to 10.2 g/dL; $P \leq .001$).

Table 2. Reasons Given for Early Termination (N = 983)

Reason	No. of Patients
Death	261
Personal	129
Intercurrent illness	106
Adverse experience	71
Inadequate response	52
Lost to follow-up	27
Abnormal laboratory result	4
Other	333
Epoetin alfa discontinued*	158
Chemotherapy discontinued	80
Disease progression	53
Unspecified	18
Bone marrow transplant scheduled	8
Surgery	8
Noncompliant	5
Other protocol	3

*Epoetin alfa discontinued because patient achieved satisfactory hemoglobin increase according to treating physician.

Table 3. Adverse Events Reported in Greater Than 5% of Patients (N = 2,030)

Event	No.	%
Disease progression	462	22.76
Neutropenia/leukopenia	191	9.41
Pyrexia	148	7.29
Thrombocytopenia	129	6.35
Nausea	122	6.01
Anemia	119	5.86
Asthenia	115	5.67

A substantial hemoglobin increase (for purposes of this analysis) was defined as an increase in hemoglobin level of at least 2 g/dL over the course of treatment without benefit of a transfusion. Overall, 53.4% of epoetin alfa–treated patients experienced a ≥ 2.0-g/dL increase in hemoglobin level. These patients were stratified by increase in hemoglobin level from baseline to week 4. Results from this analysis indicate that 75.1% of patients who achieved an increase in hemoglobin of ≥ 1.0 g/dL from baseline to week 4 of therapy experienced at least a 2.0 g/dL increase by the end of the trial; 29.5% of those patients who had a substantial increase had an increase of less than 1.0 g/dL at week 4 of the study. Prediction of a substantial increase in hemoglobin level was better in patients who did not undergo transfusion during the initial 4 weeks of the trial. Among patients who did not require transfusion during the first 4 weeks, 81.3% with an increase in hemoglobin level of ≥ 1 g/dL eventually had a substantial increase, whereas patients who underwent transfusion during this time period were less likely to have a substantial hemoglobin increase (Table 5).

Quality of Life

Of 2,030 patients, 1,498 had both baseline and termination/completion quality-of-life assessments recorded. The importance of changes in quality of life depends on both the statistical significance and the magnitude of the improvements. The magnitude was assessed using effect size. A small but important effect size is approximately 0.20; medium effect size, 0.50; and large effect size, 0.80.[25] Observed effect sizes were 0.70 for energy level, 0.55 for activity level, and 0.47 for overall quality of life, which suggests medium to large effect sizes (Table 4). Upon completion of epoetin alfa therapy, mean energy, activity, and overall quality-of-life scores were statistically significantly higher than at baseline. A direct and significant correlation was demonstrated between the magnitude of the improvement of each of the parameters of quality of life with the magnitude of the increase in the hemoglobin level from baseline (energy: $r = .30$, P

Table 4. Summary of Study Data

Variable	No. of Patients	All Patients (N = 2,030)	No. of Patients	Patients Completing (n = 1,047)
		Mean ± SD Hemoglobin (g/dL)		Mean ± SD Hemoglobin (g/dL)
Period				
Baseline	2,022	9.2 ± 1.3	1,047	9.3 ± 1.3
Month 1	2,017	10.3* ± 1.8	1,044	10.4* ± 1.7
Month 2	1,762	10.9* ± 1.9	1,042	10.9* ± 1.9
Month 3	1,470	11.1* ± 2.0	1,041	11.1* ± 2.0
Month 4	1,184	11.2* ± 2.0	1,042	11.2* ± 2.0
Baseline	2,019	9.2 ± 1.3	1,046	9.3 ± 1.3
Final	2,019	11.0* ± 2.1	1,046	11.2 ± 2.0
Change from baseline		1.8 ± 2.1		1.9* ± 2.1
		Mean ± SD Epoetin Alfa Dose (U/kg/wk)		Mean ± SD Epoetin Alfa Dose (U/kg/wk)
Month 1	2,016	442.46 ± 63.06	1,044	445.26 ± 58.01
Month 2	1,759	434.24 ± 116.02	1,042	437.98 ± 109.88
Month 3	1,469	445.56 ± 202.94	1,041	456.54 ± 197.42
Month 4	1,181	448.58 ± 228.67	1,041	456.84 ± 225.30
		Transfusion Requirements (% of patients)/mean ± SD units per patient per month)		Transfusion Requirements (% of patients)/mean ± SD units per patient per month)
Month −1	2,030	21.9%/0.57 ± 1.20	1,047	20.9%/0.52 ± 1.11
Month 1	2,030	21.9%/0.59 ± 1.25	1,047	17.8%/0.43 ± 1.01
Month 2	1,781	14.8%*/0.40* ± 1.09	1,046	12.7%*/0.35* ± 1.05
Month 3	1,474	10.7%*/0.29* ± 0.94	1,044	9.8%*/0.25* ± 0.84
Month 4	1,187	10.3%*/0.29* ± 0.99	1,045	9.4%*/0.25* ± 0.88
		Mean ± SD Visual-Analog Scores (mm)		Mean ± SD Visual-Analog Scores (mm)
Energy level				
Baseline	1,498	39.4 ± 21.3	967	40.1 ± 21.5
Termination	1,498	54.4* ± 26.5	967	58.1* ± 24.3
Effect size		.70		.83
Activity level				
Baseline	1,498	40.8 ± 23.9	967	41.3 ± 23.8
Termination	1,498	53.9* ± 27.8	967	57.6* ± 25.5
Effect size		.55		.68
Overall quality of life				
Baseline	1,498	46.4 ± 23.6	967	46.8 ± 24.0
Termination	1,498	57.4* ± 27.0	967	61.2* ± 24.7
Effect size		.47		.60

*$P < .001$.

Table 5. Prediction of Substantial Increase (≥ 2.0 g/dL) in Hemoglobin by Hemoglobin Level at 4 Weeks

	Overall Rate		Stratification by Week-4 Hemoglobin Increase			
			≥ 1.0 g/dL		< 1.0 g/dL	
Variable	No.	%	No.	%	No.	%
All patients	1,076/2,016*	53.4	792/1,054	75.1	284/962	29.5
Not transfused†	903/1,574	57.4	664/817	81.3	239/757	31.6
Transfused Patients†	173/442	39.1	128/237	54.0	45/205	22.0

*Includes patients who had baseline and month-1 hemoglobin data available.
†During the first month on study.

$< .001$; activity: $r = .28$, $P < .001$; overall quality of life, $r = .27$, $P < .001$). Figure 2 displays the changes in mean quality-of-life scores for subsets of patients with varying magnitudes of hemoglobin increase to epoetin alfa therapy. For each of the three parameters of quality of life measured, the greater the hemoglobin increase, the greater the increase in mean score observed. The only subset of patients for whom there was no significant improvement in mean quality of life were those patients who manifested a decrease in hemoglobin level during epoetin alfa therapy. For the subsets of patients who showed any increase in hemoglobin, a significant increase in mean energy, activity, and overall quality-of-life scores was observed following epoetin alfa therapy. The magnitude of the increase in mean scores was comparable to the magnitude of the hemoglobin increase for each subset. Eighty-three percent of patients were included in partitions in which a statistically significant ($P < .001$) increase in quality of life was observed.

Improvement in quality of life was observed in patients who self-administered epoetin alfa and in patients for whom epoetin alfa was administered by a health care professional. Results in both subsets of patients were similar to those observed in the overall population and there

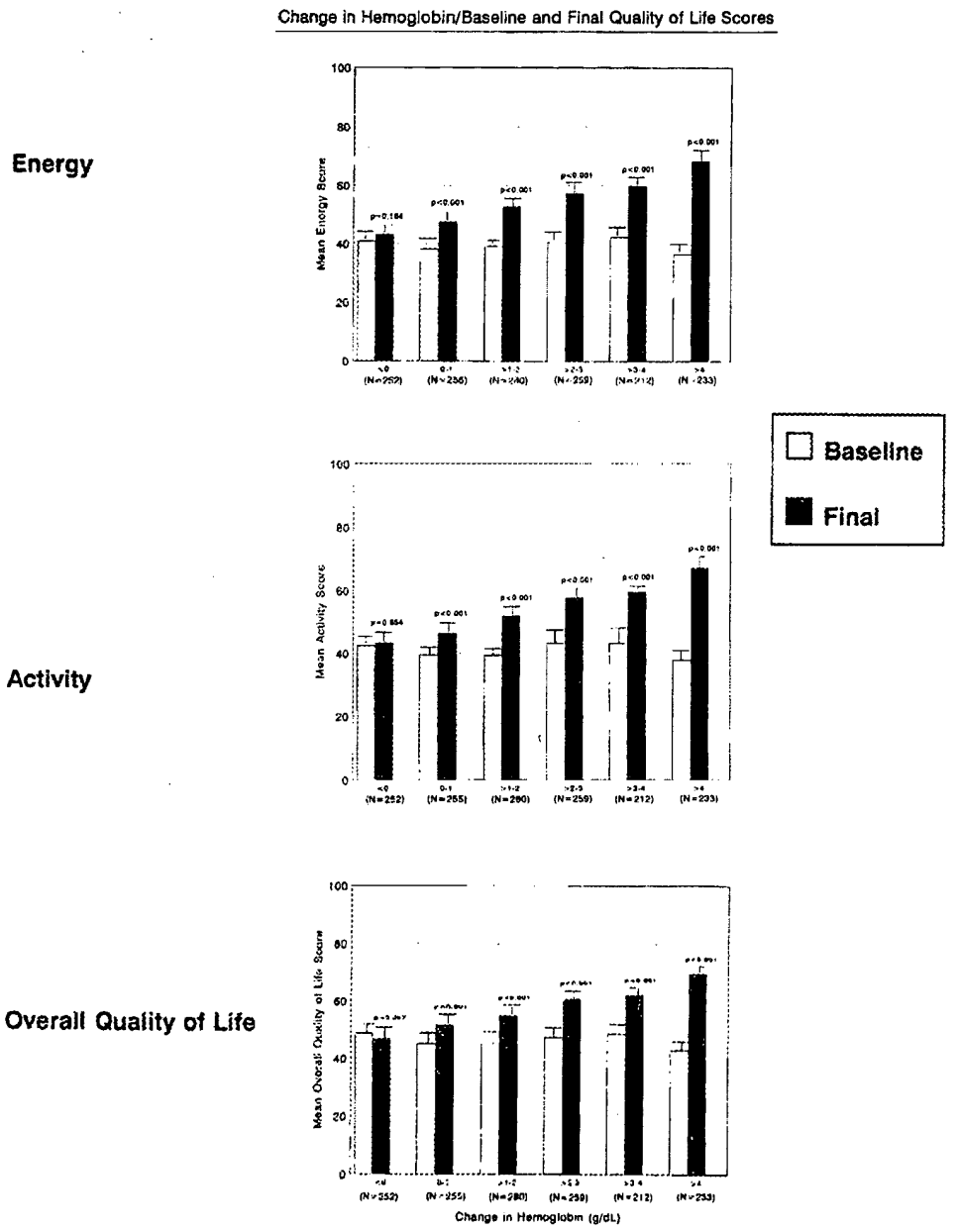


Fig 2. Changes from baseline to termination in mean quality-of-life score for subsets of patients defined by hemoglobin changes between baseline and final value. *P* values refer to paired *t* test results. Data are mean scores and upper 95% confidence intervals.

Table 6. Change From Baseline in Quality-of-Life Parameters and Hemoglobin Level by Tumor Response

Tumor Response	No. of Patients	Mean ± SD Change From Baseline in Quality-of-Life Parameters			Mean ± SD Change From Baseline in Hemoglobin (g/dL)
		Energy	Activity	Overall	
Complete	144	27.9 ± 26.3†	25.8 ± 28.4†	23.7 ± 27.3†	2.4 ± 2.1†
Partial	202	23.4 ± 27.0†	22.1 ± 28.7†	20.4 ± 28.6†	2.2 ± 2.1†
No response	124	11.8 ± 32.0†	8.1 ± 34.7*	8.0 ± 32.7*	1.6 ± 2.1†
Stable disease	30	16.1 ± 26.4*	17.4 ± 30.6*	13.8 ± 29.1*	1.5 ± 1.7†
Progressive disease	259	4.4 ± 30.2*	3.1 ± 29.9	1.0 ± 30.9	1.6 ± 2.3†

*$P < .05$.
†$P \leq .001$.

were no differences in quality-of-life scores between the two subsets.

Of 441 patients who received cisplatin-based chemotherapy, quality-of-life data were available for 316. The mean score for energy increased by 16 mm, for activity by 13 mm, and for overall quality of life by 12 mm from baseline to the measurement at the termination of epoetin alfa therapy; these increases were similar to those observed in patients who received carboplatin chemotherapy and were statistically significant ($P = .001$) when compared with pretreatment levels.

To determine the impact of tumor response and performance status on the observed improvements in quality of life during epoetin alfa therapy, a retrospective analysis was conducted. Of 759 patients included in the retrospective analysis of tumor response, treating physicians considered 144 patients to have a complete response and 202 to have a partial tumor response. No response was observed in 124 patients, 30 patients were considered to have stable disease, and 259 patients were rated as having progressive disease. Statistically significant improvement in energy ($P < .05$) was observed in all five tumor response groups. Statistically significant improvements in activity ($P < .05$) and overall quality of life ($P < .05$) were observed in patients who exhibited a complete response, partial response, no response, and stable disease. Table 6 lists changes in quality-of-life scores and hemoglobin levels stratified by tumor response. The significant improvement in energy in patients with progressive disease may be attributable to increased hemoglobin level, since a statistically significant increase in hemoglobin ($P \leq .001$) was observed in all tumor response categories. Additionally, change in quality of life was evaluated by hemoglobin change for individuals with no response, stable disease, or progressive disease. These results are presented in Fig 3 and demonstrate that quality of life improves as hemoglobin level increases in these three tumor response categories. A statistically significant correlation was observed in all three tumor response groups for energy and activity scores. For individuals with progressive disease, a statistically significant correlation was found between hemoglobin level and overall quality of life.

Using regression analysis to adjust for the possible effect of tumor response, a significant correlation of change in hemoglobin and improvement in quality-of-life parameters was demonstrated (energy: partial $r = .257$, $P < .001$; activity: partial $r = .207$, $P < .001$; overall quality of life: partial $r = .190$, $P < .001$). Statistically significant correlations between tumor response and improvements in energy ($r = -.13$, $P = .006$), activity ($r = -.10$, $P = .032$), and overall quality of life ($r = -.13$, $P = .010$) were also demonstrated. Thus, both tumor response and change in hemoglobin level were independently correlated with improved quality of life and the improvement in quality of life associated with increased hemoglobin levels was not an epiphenomenon related to tumor response. Moreover, hemoglobin improved significantly in all tumor response categories and appeared to be approximately twice as strongly correlated with improved quality-of-life scores as tumor response alone.

Eastern Cooperative Oncology Group (ECOG) and Karnofsky scores were also collected and analyzed in the retrospective analysis. Overall, the baseline ECOG score was 1.8 and the final score was 1.9 (n = 624). No correlation between change in hemoglobin level and change in ECOG score from baseline to final was observed ($r = .01$, $P = .858$). Overall, the baseline Karnofsky score was 73.7 and the final score was 73.2 (n = 697). With this parameter, a significant correlation between change in hemoglobin level and change in Karnofsky score was observed ($r = .17$, $P < .001$). In patients whose hemoglobin level increased less than 2 mg/dL, there was a decrease in mean Karnofsky score, whereas an increase in mean Karnofsky score was observed in patients whose hemoglobin level increased at least 2 g/dL from baseline.

Transfusion Requirements

The transfusion requirements for the month before study entry and the 4 months of epoetin alfa therapy are shown in Fig 4 and Table 4. Significantly fewer ($P <$

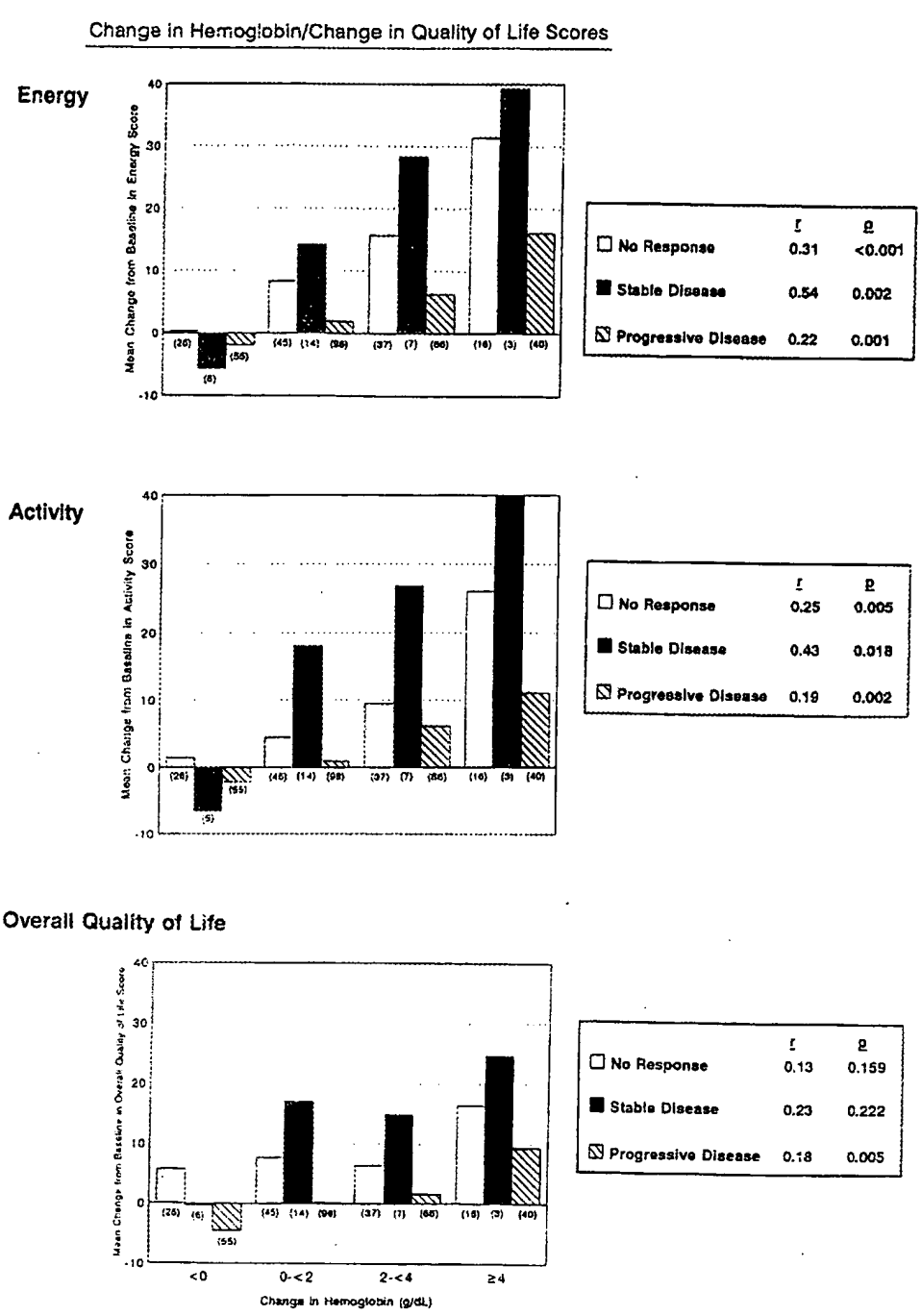


Fig 3. Mean change from baseline to termination in quality-of-life scores for subsets of patients defined by change in hemoglobin. Data are for patients judged to have no response to chemotherapy, stable disease, and progressive disease. Number of patients in each group is given in parenthesis.

.001) patients were transfused and fewer transfusions were administered per patient per month after the first month of epoetin alfa therapy and this decrease was maintained throughout the 4 months of the study. Epoetin alfa was associated with approximately a 50% decrease in both the proportion of patients who required transfusion and in the number of units of RBCs transfused per patient per month.

Improvement in transfusion requirement was apparent in patients with hematologic, as well as nonhematologic malignancies. Results in these two subsets were similar to overall results and no differences in transfusion requirements between the two subgroups were observed.

Of 445 patients who required transfusion during the first month of epoetin alfa therapy, 379 had transfusion data available for subsequent months. Of these 379, 58%

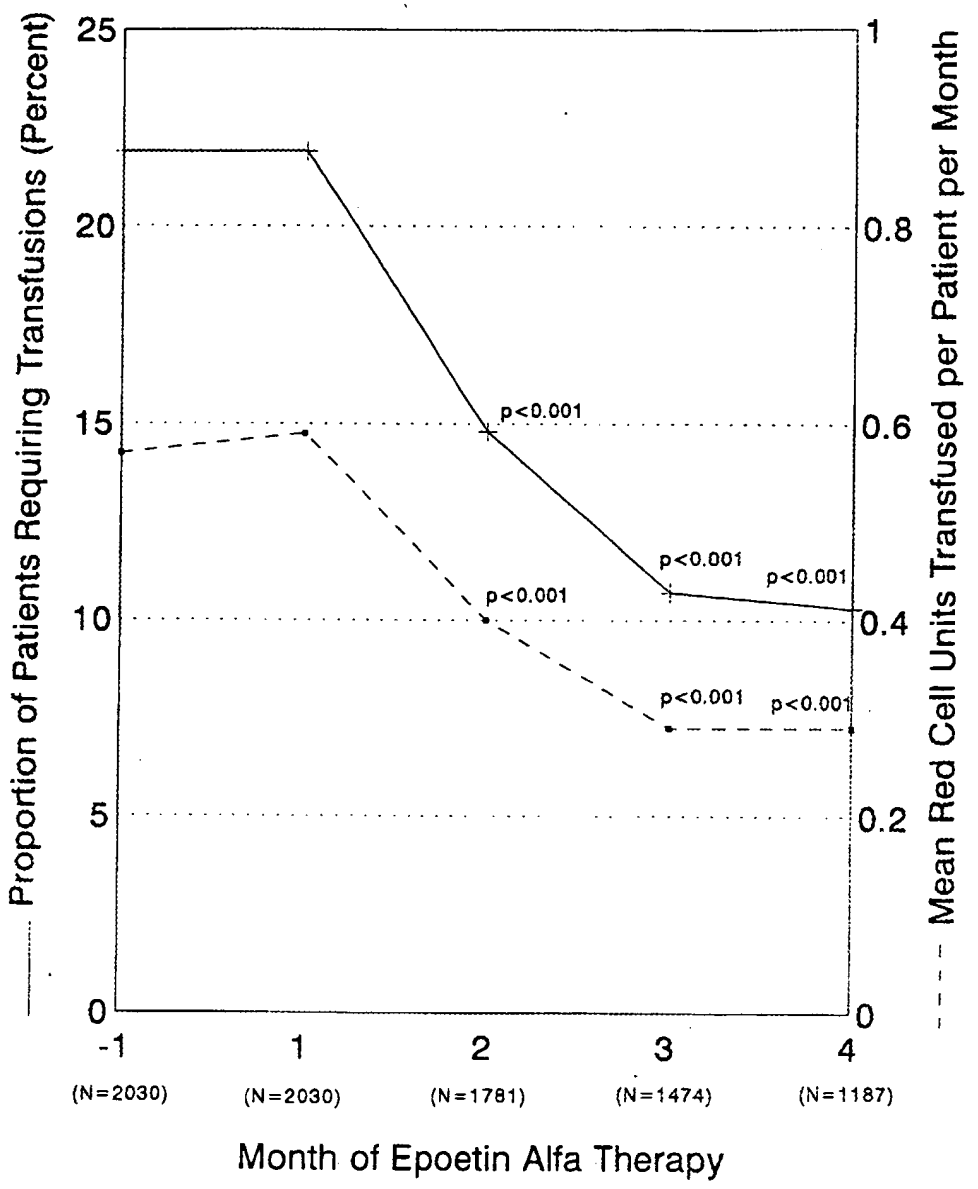


Fig 4. Proportion of patients transfused and number of units transfused per patient for the month before initiation of epoetin alfa therapy and during treatment. *P* values refer to comparisons of each value to baseline using McNemar's χ^2 test.

did not require a transfusion after the first month of epoetin alfa therapy. Of 1,402 patients who did not require transfusion during the month before epoetin alfa was initiated, 1,156 (82%) remained transfusion-independent after the first month of therapy (Table 7). Baseline and final hemoglobin values for this group of patients were 9.3 and 11.5 g/dL, respectively ($P < .001$).

Study termination rates were similar for transfusion-dependent and transfusion-independent patients. Overall, 48% of transfusion-independent patients and 51% of transfusion-dependent patients prematurely discontinued study participation.

Additionally, the relationship of baseline transfusion status to tumor type and chemotherapeutic regimens was evaluated. Percentages of baseline transfusion-dependent and transfusion-independent patients were comparable in patients with hematologic and nonhematologic malignancies and in patients who received cisplatin, carboplatin, and nonplatinum chemotherapy.

Although recommended by the protocol and product labeling, physicians did not always take the opportunity to increase the starting dose of epoetin alfa administered to patients who remained transfusion-dependent. Of 1,047 patients who completed 4 months of therapy with epoetin alfa, 233 received one or more transfusions during epoetin alfa therapy. For 119 (51.1%) of these patients, the dose

Table 7. Transfusion-Independent/Dependent Status at Baseline and On-Study

	On-Study (after month 1)			
	Independent		Dependent	
Baseline (month 1)	No.	%	No.	%
Independent (N = 1,402)	1,156	82	246	18
Dependent (N = 379)	218	58	161	42

Note. A total of 249 (12%) of 2,030 patients only had month-1 transfusion data and were not assessable.

of epoetin alfa was not adjusted or was decreased. For the remainder of these patients, the treating physician increased the dose of epoetin alfa. The mean weekly dose of epoetin alfa administered to these patients who were transfusion-dependent on epoetin alfa therapy was 508.4 U/kg (SD, 120.9; range, 202.5 to 837 U/kg/wk).

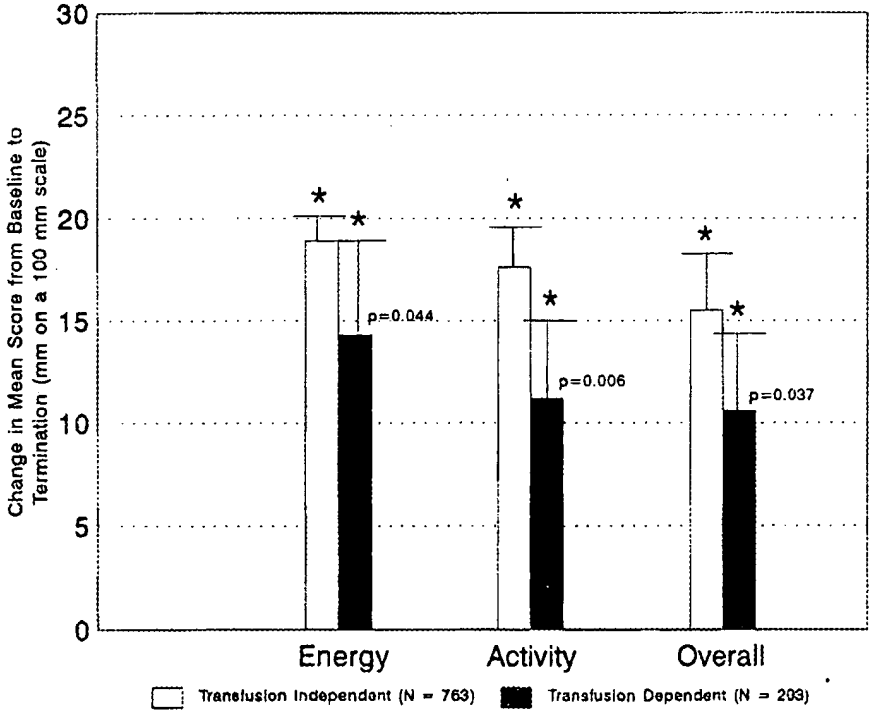
The changes in quality-of-life parameters measured during epoetin alfa therapy were of a significantly lower magnitude for patients who received transfusions compared with those who were not transfused during therapy (Fig 5). Nevertheless, statistically significant increases in the mean scores for all three quality-of-life parameters were observed in the subset of patients who received transfusions during epoetin alfa therapy. In addition, the increase in score correlated with increases in mean hemoglobin concentration.

Completers

The changes in hemoglobin level, epoetin alfa dose, transfusion requirements, and visual-analog scores for all treated patients and for the subset that completed 4 months of epoetin alfa therapy are listed in Table 4. The data for completers are similar to the data for all patients, which reflects the absence of a patient-selection effect of patients who discontinued therapy. Note that the mean dose of epoetin alfa was less than the 450-U/kg/wk recommended starting dose throughout the study, even though it was recommended that the dose be increased for failure to respond and a significant number of patients remained transfusion-independent throughout the study.

DISCUSSION

The safety and efficacy of new therapeutic agents are usually demonstrated in placebo-controlled clinical trials prior to their use in the community. In the setting of postrelease use in community practice, new therapies may not always have the same benefits and safety profiles observed in the carefully regulated studies. Unfortunately, the practice patterns and clinical results with respect to new agents introduced into community oncology practice are rarely investigated in large effectiveness studies. This lack of data impairs realistic and relevant cost analyses, the design of future clinical trials, and the appropriate usage guidelines.



* p≤0.001 within group change from baseline

Fig 5. Changes in mean quality-of-life parameters for the 966 completed patients who had baseline and termination quality-of-life and transfusion data. *P* values reflect unpaired *t* tests comparing changes in mean values based on transfusion status after 1 month of therapy. Data are changes in mean score and upper 95% confidence intervals.

In phase III placebo-controlled studies, epoetin alfa has been shown to increase hemoglobin levels, decrease transfusion requirements, and improve self-perceived quality-of-life parameters in anemic patients undergoing cancer chemotherapy.[4,12,13] The study presented demonstrates that in the setting of community oncology practice, epoetin alfa during chemotherapy of anemic cancer patients is associated with an increase in hemoglobin concentration, a decrease in RBC transfusion requirements, and an improvement in self-perception of quality-of-life parameters, including energy level, activity level, and overall quality of life. These effects were observed in a setting in which physicians were provided with guidelines for epoetin alfa therapy reflective of the package insert, but were not required to follow a rigidly regulated treatment or transfusion protocol. The data were generated at more than 500 community oncology practices and included more than 2,000 patients with a wide spectrum of malignancies undergoing therapy with a variety of different chemotherapy regimens. The practice patterns observed in this study are therefore likely to be reflective of the use of epoetin alfa during cancer chemotherapy in the community, and our results may more realistically predict the clinical effects of epoetin alfa use in current oncology practice.

The data presented suggest an aspect of current physician behavior with respect to the anemic cancer patient that merits special comment. Our study patients had significantly higher hemoglobin levels after the initiation of epoetin alfa, which were associated with a significant improvement in quality of life. These data suggest that this improvement in quality of life was directly related to the increased hemoglobin level (Fig 2). In the open-label multicenter study of 1,004 dialysis patients previously mentioned,[15] epoetin alfa was associated with a substantial and significant improvement in the health-related quality-of-life components of physical functioning, vitality, social functioning, and mental health. These data demonstrate the effectiveness of epoetin alfa as used in clinical practice and suggest that the beneficial quality-of-life effects observed were mediated through change in hemoglobin level. Data from this large study corroborate our findings.

Evaluation of the impact of tumor response on quality of life demonstrated that all patients, regardless of tumor response, exhibited a statistically significant increase in energy level. The unexpected observed improvement in energy for patients with progressive disease may be attributable to increased hemoglobin level, since a statistically significant increase in hemoglobin ($P \leq .001$) was observed in all tumor response categories, including patients with progressive disease.

To eliminate the variable of partial or complete remission of disease, separate correlations were performed for patients with no response to chemotherapy, stable disease, or progressive disease. Results of this analysis strengthened the conclusion that improving anemia with epoetin alfa improves quality of life, even in patients with a severe and progressing illness.

Treating physicians may therefore underestimate the negative impact of anemia on the functional status of patients during cancer chemotherapy, and the potential for increasing quality of life in these patients by aggressively treating anemia, whether RBC transfusions or epoetin alfa are used to achieve this end. A positive correlation between an increase in hemoglobin level and improvement in quality of life is important, and the impact of anemia on quality of life merits more careful study to confirm our observations and to suggest a target optimal hemoglobin level for the anemic cancer patient.

This observed impact of epoetin alfa on the self-perceived well-being of cancer patients undergoing myelosuppressive chemotherapy is central to evaluation of its therapeutic usefulness. Using effect size calculations, the magnitude of the changes in perceived quality of life were compared with those for traditional management of cancer pain. Effect sizes have been shown to be a useful tool for interpretation of clinically meaningful change by providing a standardized measure of change in a group or a difference in changes between two groups.[26] Effect sizes were calculated from the published literature for oral dipyrone[27] (3.72), rectal morphine[28] (1.65), and controlled-release morphine[29] (0.78). Effect sizes of ≥ 1.0 are large and seen in dramatic interventions, eg, functional improvement following hip replacement surgery. The effects sizes found for epoetin alfa were in the medium to large range (ranging from 0.70 for energy level to 0.47 for overall quality of life) and approached those found for cancer pain management. The linear-analog scale used in this study has been shown to be sensitive in capturing systematic and important differences in patient quality of life.[16,17] Improvement in quality of life associated with epoetin alfa treatment is an important outcome, which demonstrates that the patients' functional status and well-being is enhanced even in view of chronic disease and intensive chemotherapy. A subjective improvement in sense of well-being may motivate patients to adhere to rigorous chemotherapy and treatment regimens. Improvement in patients' quality of life may also be a meaningful outcome for families of cancer patients who often provide support during treatment.

Although several studies, including the large community-based study reported here, have demonstrated that

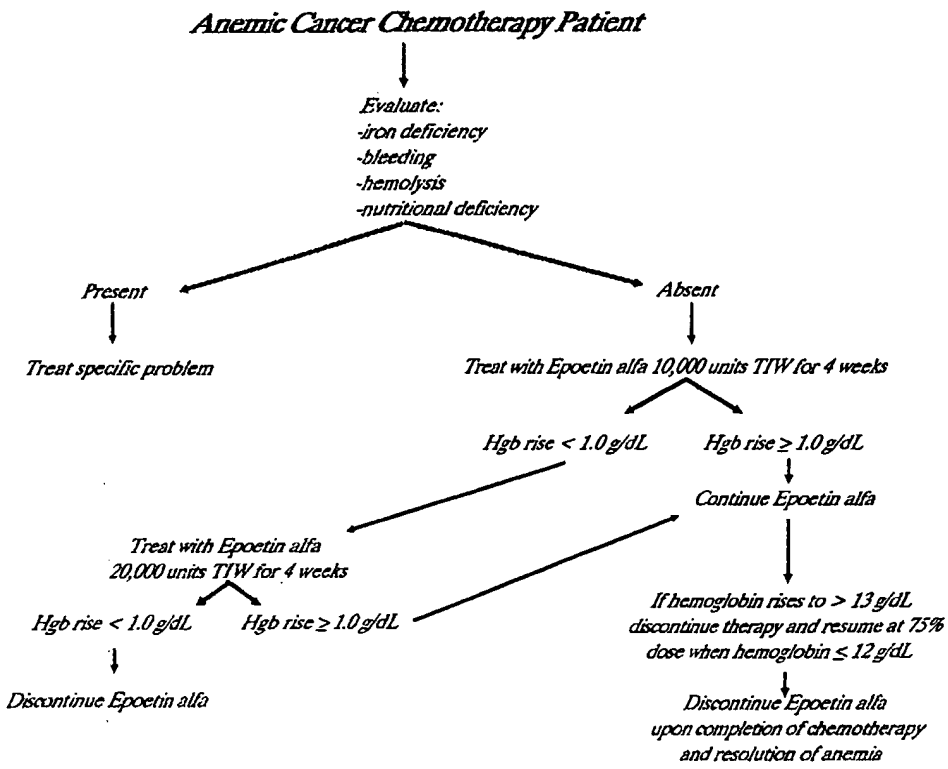


Fig 6. Suggested treatment algorithm for the use of epoetin alfa in the management of anemic patients undergoing cancer chemotherapy.

NOTE: *Prior to and during Epoetin alfa therapy, the patient's iron stores should be evaluated. Virtually all patients will eventually require supplemental iron to adequately support erythropoiesis stimulated by Epoetin alfa.*

epoetin alfa has efficacy in the treatment of anemic cancer patients during chemotherapy, the pharmacoeconomics of epoetin alfa use in this setting has not yet been adequately explored. Factors that have an impact on pharmacoeconomics include the identification of predictors of epoetin alfa response that could be used either to focus the initiation of therapy on patients who will benefit or to discontinue its use early in patients who are not benefiting,[30] the optimal dose and schedule of epoetin alfa, and the true costs associated with RBC transfusions, including the costs of the blood products and their administration, immunologic and infectious complications, and the effects, if any, of transfusion-associated immunosuppression on the natural history of a particular malignancy.

Information was obtained from this study that will aid in the development of improved treatment guidelines for anemic cancer patients receiving chemotherapy. Predicting responsiveness to epoetin alfa in cancer patients is an important medical, as well as economic issue for the clinician. Allowing clinicians to identify those patients who are unlikely to respond to epoetin alfa early in the course of treatment by implementing usage guidelines supports the appropriate use of the product. The study showed that overall, 53.4% of epoetin alfa–treated patients had a substantial hemoglobin increase (defined as a ≥ 2-g/dL increase without benefit of transfusion) over the course of therapy. This group of patients was then stratified by hemoglobin increase from baseline to week 4. Results from this analysis indicated that 75.1% of patients who achieved an increase in hemoglobin level of ≥ 1.0 g/dL from baseline to week 4 of therapy had a substantial hemoglobin increase by the end of the trial, whereas only 29.5% of patients who had an increase of less than 1.0 g/dL eventually achieved a substantial increase. By examining changes in hemoglobin level after only 4 weeks of epoetin alfa administration, it appears possible to predict which patients are most or least likely to have a substantial hemoglobin increase. The ability to predict this increase early during the course of epoetin alfa treatment may theoretically provide the clinician with a strategy to improve clinical outcomes in anemic cancer patients receiving chemotherapy in a more timely manner.

The optimal dose and schedule of epoetin alfa remain to be characterized; in this study, and in studies that have used similar doses and schedules, approximately 50% to 60% of patients demonstrate a substantial (≥ 2.0 g/dL)

increase in hemoglobin level. More patients may achieve substantial increases in hemoglobin levels when higher doses of epoetin alfa are administered. The use of higher doses of epoetin alfa in patients who do not exhibit an adequate increase in hemoglobin level with the recommended dose will be associated with higher drug acquisition costs, but may produce a substantial hemoglobin increase and decrease both the number of transfusions required and the number of doses of epoetin alfa given that do not produce a clinical benefit. The actual short- and long-term resource consumption associated with each RBC transfusion is the subject of ongoing studies; these data will be essential in future cost analyses of epoetin alfa in this setting, once the most efficient doses, schedules, and targets of therapy are determined. Finally, future studies need to confirm the observed impact of anemia on the quality of life of patients receiving cancer chemotherapy. These studies will help to determine the target hemoglobin levels for these patients to optimize quality of life and functional capacity. Once an appropriate target hemoglobin level can be established, the relative costs and quality-of-life effects of transfusion and epoetin alfa therapy in maintaining this level can be determined.

Data presented in this study suggested that participating physicians did not increase the dose of epoetin alfa in patients who did not exhibit an increase in hemoglobin level or even in those who remained transfusion-dependent during therapy. Therefore, development of specific treatment guidelines for epoetin alfa use is important to optimize appropriate use given the data currently available. Although much more remains to be learned about the most effective use of epoetin alfa during cancer chemotherapy, a proposed treatment algorithm is presented in Fig 6. Patients should be evaluated for causes of anemia such as nutritional deficiency before epoetin alfa is instituted. The initial recommended dose of epoetin alfa is 10,000 U subcutaneously thrice weekly (150 U/kg for a 70-kg patient). The physician should consider increasing the dose to a maximum of 20,000 U thrice weekly (300 U/kg for a 70-kg patient) in patients who do not respond to the initial dose with an increase in hemoglobin level of at least 1 g/dL after 4 weeks of therapy. A patient who does not respond to 20,000 U thrice weekly is unlikely to respond to higher doses.

Before and during epoetin alfa therapy, the patient's iron stores should be evaluated. Virtually all patients will eventually require supplemental iron to support adequately erythropoiesis stimulated by epoetin alfa.

We conclude that, in the setting of community oncology practice, epoetin alfa is effective in increasing hemoglobin level, decreasing transfusion requirements, and, most importantly, improving functional status and quality of life in anemic cancer patients undergoing myelosupressive chemotherapy. Improvement in quality of life can be attributed to increased hemoglobin level, independent of tumor response. These data indicate that epoetin alfa can provide important therapeutic benefit and anemia in this group of patients should be aggressively treated. Patients likely to benefit from epoetin alfa can be identified in the early phase of epoetin alfa therapy and guidelines for efficient and economically sound use of epoetin alfa are possible.

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